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# A terminal metabolite of niacin promotes vascular inflammation and contributes to cardiovascular disease risk

Marc Ferrell<sup>1 2</sup>, Zeneng Wang<sup>1</sup>, James T Anderson<sup>1</sup>, Xinmin S Li<sup>1</sup>, Marco Witkowski<sup>1 3</sup>, Joseph A DiDonato<sup>1</sup>, James R Hilser<sup>4 5</sup>, Jaana A Hartiala<sup>4</sup>, Arash Haghikia<sup>3 6 7 8 9</sup>, Tomas Cajka<sup>10 11</sup>, Oliver Fiehn<sup>10</sup>, Naseer Sangwan<sup>1</sup>, Ilja Demuth<sup>12 13</sup>, Maximilian König<sup>12</sup>, Elisabeth Steinhagen-Thiessen<sup>12</sup>, Ulf Landmesser<sup>3 6 7 8 9</sup>, W H Wilson Tang<sup>1 14</sup>, Hooman Allayee<sup>4 5</sup>, Stanley L Hazen<sup>15 16</sup>

Affiliations

## Affiliations

- 1 Department of Cardiovascular & Metabolic Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA.
- 2 Systems Biology and Bioinformatics Program, Department of Nutrition, Case Western Reserve University, Cleveland, OH, USA.
- 3 Department of Cardiology, Angiology and Intensive Care, Deutsches Herzzentrum der Charité, Campus Benjamin Franklin, Berlin, Germany.
- 4 Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA.
- 5 Department of Biochemistry & Molecular Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA.
- 6 German Center for Cardiovascular Research (DZHK), Partner Site Berlin, Berlin, Germany.
- 7 Berlin Institute of Health (BIH), Berlin, Germany.
- 8 Friede Springer Cardiovascular Prevention Center at Charité, Berlin, Germany.
- 9 Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany.
- 10 West Coast Metabolomics Center, University of California, Davis, Davis, CA, USA.
- 11 Institute of Physiology of the Czech Academy of Sciences, Prague, Czech Republic.
- 12 Department of Endocrinology and Metabolism, Charité - Universitätsmedizin Berlin, Berlin, Germany.
- 13 Berlin Institute of Health Center for Regenerative Therapies, Berlin, Germany.
- 14 Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, OH, USA.
- 15 Department of Cardiovascular & Metabolic Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA. hazens@ccf.org.
- 16 Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, OH, USA. hazens@ccf.org.

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## Abstract

Despite intensive preventive cardiovascular disease (CVD) efforts, substantial residual CVD risk remains even for individuals receiving all guideline-recommended interventions. Niacin is an essential micronutrient fortified in food staples, but its role in CVD is not well understood. In this study, untargeted metabolomics analysis of fasting plasma from stable cardiac patients in a prospective discovery cohort (n = 1,162 total, n = 422 females) suggested that niacin metabolism was associated with incident major adverse cardiovascular events (MACE). Serum levels of the terminal metabolites of excess niacin, N1-methyl-2-pyridone-5-carboxamide (2PY) and N1-methyl-4-pyridone-3-carboxamide (4PY), were associated with increased 3-year MACE risk in two validation cohorts (US n = 2,331 total, n = 774 females; European n = 832 total, n = 249 females) (adjusted hazard ratio (HR) (95% confidence interval) for 2PY: 1.64 (1.10-2.42) and 2.02 (1.29-3.18), respectively; for 4PY: 1.89 (1.26-2.84) and 1.99 (1.26-3.14), respectively). Phenome-wide association analysis of the genetic variant rs10496731, which was significantly associated with both 2PY and 4PY levels, revealed an association of this variant with levels of soluble vascular adhesion molecule 1 (sVCAM-1). Further meta-analysis confirmed association of rs10496731 with sVCAM-1 (n = 106,000 total, n = 53,075 females, P = 3.6 × 10<sup>-18</sup>). Moreover, sVCAM-1 levels were significantly correlated with both 2PY and 4PY in a validation cohort (n = 974 total, n = 333 females) (2PY: rho = 0.13, P = 7.7 × 10<sup>-5</sup>; 4PY: rho = 0.18, P = 1.1 × 10<sup>-8</sup>). Lastly, treatment with physiological levels of 4PY, but not its structural isomer 2PY, induced expression of VCAM-1 and leukocyte adherence to vascular endothelium in mice. Collectively, these results indicate that the terminal breakdown products of excess niacin, 2PY and 4PY, are both associated with residual CVD risk. They also suggest an inflammation-dependent mechanism underlying the clinical association between 4PY and MACE.

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